CROSS REFERENCES TO RELATED APPLICATIONS

This application is a continuation of PCT JP00/05665, which was filed August 23, 2000, and which is incorporated herein by reference in its entirety.

IN THE CLAIMS

Please amend the claims as shown on the attached marked-up copy to read as follows.

1. (Amended) A method for producing N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, comprising:

(1) subjecting N-L-α-aspartyl-L-phenylalanine 1-methyl ester and 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or a derivative thereof to reductive alkylation in a solvent to obtain N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

(2) crystallizing said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester,

wherein said reductive alkylation comprises catalytic hydrogenation, and

wherein said derivative thereof is selected from the group consisting of

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)-2-propenylaldehyde, and

acetals derived therefrom.

2. (Amended) The method of Claim 1, wherein said crystallizing said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester comprises any one of the following crystallization methods:

a. crystallization with a solvent useful for crystallization;

b. crystallization after extraction with water; and

c. crystallization after separation of N-L-α-aspartyl-L-phenylalanine 1-methyl ester.

3. (Amended) A method for purifying N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, which comprises:

subjecting a composition which comprises N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester and at least one compound selected from the group consisting of N-L-α-aspartyl-L-phenylalanine 1-methyl ester, a peptide derivative, an amino acid, an amino acid derivative, an aldehyde, an acetal and an alcohol derivative as impurity to at least any one of the following crystallization processes:

a. crystallization with a crystallization solvent;

b. crystallization after extraction with water; and

c. when said composition comprises N-L-α-aspartyl-L-phenylalanine 1-methyl ester, further crystallization after said N-L-α-aspartyl-L-phenylalanine 1-methyl ester has been separated,

to obtain crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

4. (Amended) The method of Claim 1, wherein said solvent for said reductive alkylation reaction is at least one solvent selected from the group consisting of alcohols,

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tetrahydrofuran, acetonitrile, toluene, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

5. (Amended) The method of Claim 2, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized by a process of concentration or by a process for solvent substitution.

6. (Amended) The method of Claim 1, wherein said solvent for said crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

7. (Amended) The method of Claim 1, wherein said solvent for said crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is the same solvent which has been used in the reductive alkylation reaction.

8. (Amended) The method of Claim 5, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized by solvent substitution using at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

9. (Amended) The method of Claim 1, wherein said solvent of said reductive alkylation reaction is one or more alocohols or a mixed solvent of one or more alcohols and water, and the solvent of said crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is one or more alcohols or a mixed solvent comprising one or more alcohols.

10. (Amended) The method of Claim 2, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after extraction with water using at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

11. (Amended) The method of Claim 2, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after extraction with water and said extraction with water is conducted with a mixed solvent which comprises water and one or more organic solvents, wherein said organic solvent forms a layer which separates from an aqueous layer upon mixture with water, and said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is extracted into the aqueous layer.

12. (Amended) The method of Claim 11, wherein said organic solvent is at least one solvent selected from the group consisting of acetic acid esters, ether, chloroform, dichloromethane, hexane, toluene, alcohols, tetrahydrofuran, acetone, acetonitrile and acetic acid.

13. (Amended) The method of Claim 2, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after having separated N-L-α-aspartyl-L-phenylalanine 1-methyl ester and is crystallized from at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

14. (Amended) The method of Claim 2, wherein said process for separating N-L-α-aspartyl-L-phenylalanine 1-methyl ester is a process for separating N-L-α-aspartyl-L-phenylalanine 1-methyl ester by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid esters, ether, chloroform, dichloromethane, hexane, toluene, alcohols, tetrahydrofuran, acetone, acetonitrile, acetic acid and water.

15. (Amended) The method of Claim 1, wherein said reductive alkylation reaction is conducted in at least one organic solvent which dissolves the starting materials or a mixed solvent of said organic solvents and water, and when an insoluble material is present in the reaction mixture obtained after said reductive alkylation reaction, said insoluble material is separated by filtration.

17. (Amended) The method of Claim 1, wherein said catalytic hydrogenation is conducted in the presence of at least one catalyst selected from the group consisting of palladium, platinum, and rhodium based catalysts.

18. (Amended) The method of Claim 1, wherein said catalytic hydrogenation is conducted at a hydrogen pressure of 0.1 to 1 MPa.

19. (Amended) The method of Claim 1, wherein said reductive alkylation reaction is conducted at a temperature range of from 15 to 50 °C, and a reaction time of from 2 to 48 hours.

20. (Amended) The method of Claim 1, wherein said reductive alkylation reaction is carried out in a reaction solvent having a pH of from 4 to 6.5.

21. (Amended) The method of Claim 1, wherein the molar ratio of said N-L-α-aspartyl-L-phenylalanine 1-methyl ester to said 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or derivative thereof ranges from 0.5 to 2.

22. (Amended) The method of Claim 3, wherein said aldehyde is selected from the group consisting of:

3-(3-methoxy-4-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protectedhydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protectedhydroxyphenyl)-2-propenylaldehyde,

and said acetal comprises any acetal derived from these aldehydes.

23. (Amended) Crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, which is prepared by the process of Claim 1.

24. (Amended) Crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, which exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° with CuKα rays.

26. (Amended) The crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester of Claim 23, which is obtained upon crystallization of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester from at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

27. (Amended) A sweetening agent, a food and drink, a medicament, a confectionary, a hygienic article, or a sweetened food and drink for mammals comprising said crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester of Claim 23.

28. (Amended) A sweetener comprising said crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester of Claim 23 and at least one adjunct selected from the group consisting of a carrier, a bulking agent and excipient, which is employed in sweetening materials.

29. (Amended) The method of Claim 1, wherein said 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde or derivative thereof is prepared by subjecting 3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde or an acetal thereof, wherein the hydroxyl group may be protected, to reduction to obtain said 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde or derivative thereof.

30. (Amended) The method of Claim 29, wherein said reduction is conducted in the presence of a reduction catalyst or a rhodium based catalyst.

31. (Amended) The method of Claim 3, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized by a process of concentration or by a process for solvent substitution.

32. (Amended) The method of Claim 3, wherein said crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is carried out in at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

33. (Amended) The method of Claim 2, wherein said crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is carried out in the same solvent which has been used in said reductive alkylation reaction.

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34. (Amended) The method of Claim 31, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized by solvent substitution using at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

35. (Amended) The method of Claim 2, wherein said solvent of the reductive alkylation reaction is one or more alcohols or a mixed solvent of one or more alcohols and water, and the solvent of the crystallization of said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is one or more alcohols or a mixed solvent comprising one or more alcohols.

36. (Amended) The method of Claim 3, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after extraction with water using at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

37. (Amended) The method of in Claim 3, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after extraction with water and said extraction with water is conducted with a mixed solvent which comprises water and one or more organic solvents, wherein said organic solvent forms a layer which separates from an aqueous layer upon mixture with water, and said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is extracted into the aqueous layer.

38. (Amended) The method of Claim 3, wherein said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is crystallized after having separated N-L-α-aspartyl-L-phenylalanine 1-methyl ester and is crystallized from at least one solvent selected from the group consisting of alcohols, tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid, acetic acid esters, and mixed solvents which comprise at least one of these organic solvents and water.

39. (Amended) The method of Claim 3, wherein said process for separating N-L-α-aspartyl-L-phenylalanine 1-methyl ester is a process for separating N-L-α-aspartyl-L-phenylalanine 1-methyl ester by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid esters, ether, chloroform, dichloromethane, hexane, toluene, alcohols, tetrahydrofuran, acetone, acetonitrile, acetic acid and water.

Please cancel Claims 16 and 25, without prejudice toward the further prosecution of this claim in a continuation and/or divisional application.

SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 1 to incorporate the limitations of Claim 16 and to recite "wherein said reductive alkylation comprises catalytic hydrogenation." Support for amended Claim 1 can be found in Claims 1, 15, and 16, and as originally filed. Applicants have also amended Claims 2-15, 17-24, and 26-39, such that they are free of the criticisms outlined on pages 3-6 of the Official Action. Support for amended Claims 2-15, 17-24, and 26-39 can be found in the same claims, as originally filed.